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RELATION OF FEVER TO ENERGY EXPENDITURE.(U)
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Fort Detrick, Frederick, Maryland 21701

An Invited Presentation for a Conference on:

THE ASSESSMENT OF ENERGY METABOLISM IN HEALTH AND DISEASE

Chaired By: John M. Kinney, M.D.

Hamish N. Munro, D.Sc.

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Sponsored By: Ross Laboratories, a Division of Abbott Laboratories, Columbus, Ohio

To be held at: Black Point Inn, Prouts Neck, Maine, 25-28 June 1978

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The febrile response has close and important relationships with cellular mechanisms that regulate energy expenditures within the body. Many important concepts about energy metabolism were first set forth by Max Rubner (1902) in his monograph, "Laws of Energy Consumption in Nutrition." Comprehensive data on patients with febrile illnesses were subsequently accumulated when the clinical calorimetry laboratories were established at the Russell Sage Institute of Pathology at Bellevue Hospital. These unique facilities were used by such men as DuBois, Coleman, McCann, Barr, and Cecil, who collectively must be ranked among the "all-time greats" in American medicine. More recent studies have attempted to determine the molecular basis for the relationships between fever and energy expenditure in terms of their biochemical, physiological, hormonal and nutritional aspects.

INCREASED OXYGEN CONSUMPTION

Oxygen consumption measurements were initially obtained in patients with a diverse variety of febrile illnesses, including tuberculosis, typhoid fever, malaria, bacterial pneumonia and other coccal infections, rheumatoid arthritis, and rheumatic fever, and published as part of a comprehensive series of calorimetry papers (Barr and DuBois, 1918; McCann and Barr, 1920; Barr et al, 1922; Colemen et al, 1922). These combined studies indicated that up to a 13% increase in metabolic rates could be expected for each degree Celsius of increase in body temperature (Lusk, 1928; DuBois, 1936).

Comparable increases in the metabolic rates were found to occur during artifically induced fevers caused by an inoculation of bacterial

endotoxin (Grollman, 1929) or the use of hyperthemia cabinets (Altschule and Freedburg, 1945). Similar increases in oxygen consumption during fever have also been shown in a variety of animal studies (Greiff and Pinkerton, 1948) including such relatively simple models as the inoculation of chicken eggs with typhus fever rickettsiae (Hermreck and Thal, 1969). In recent years, several groups have measured the increase in oxygen consumption of patients with surgical sepsis (Clowes et al, 1966; Kinney et al, 1970; Halmagyi et al, 1974, Wilmore, 1977) in an attempt to improve the clinical management of these patients.

In the absence of an increased intake of food (or more frequently, in the presence of a diminished caloric intake), the increase in oxygen consumption during periods of fever serves to indicate that both the production and utilization of energy-yielding substrates, derived from body sources, are accelerated to meet the needs of heightened cellular metabolism. The physiological and molecular mechanisms by which these processes are accomplished during periods of fever have been subjected to extensive studies in man and experimental animals, and have been reviewed in considerable detail during a recent workshop (Beisel et al, 1977).

UNDERLYING CONTROL MECHANISMS

Several broad principles are helpful in explaining the mechanistic basis for the increased production and utilization of the metabolizable, energy-yielding substrates made available to cells during periods of fever.

First, the generalized metabolic responses of liver, muscle, and other body cells during periods of acute fever are relatively stereotyped despite any differences in the inciting causes, i.e., infectious microorganisms, toxins, sterile inflammatory responses, or artificially induced hyperthermia.

Second, metabolic pathways normally present in body cells are utilized to provide the energy-yielding substances needed to maintain febrile hypermetabolism. Although the use of certain biochemical pathways may be accentuated, there is no evidence, despite extensive searches, to indicate disruption of the basic, normal molecular machinery available within cells, at least during the early stages of a febrile process. It is only during the terminal stages of an overwhelmingly severe infection, or in the presence of hepatocellular damage or necrosis as a direct result of invading microorganisms or their toxins, that evidence emerges to suggest the pathological disruption of energy-generating metabolic machinery.

Third, the observed changes in energy production and utilization are regulated by a combination of both hormonal effects and the availability of various substrates. In some instances, the hormonal effects seem to predominate, while at other times, the presence or absence of a key substrate has a major controlling influence.

Fourth, although the body is capable of utilizing its normally available substrates for the production of cellular energy, most of the extra metabolizable energy needed during fever is derived from the accelerated utilization of glucose. The increase in energy availability

during periods of fever is therefore based upon glycogenolysis, and more importantly, upon accelerated gluconeogenesis. The accelerated production of glucose is supported to a large degree by amino acids made available through the degradation of somatic proteins and the increased production in skeletal muscle of the gluconeogenic amino acids, alanine and glutamine.

While these several general concepts represent an important statement concerning our present understanding about body energy metabolism during fever, they must be interpreted and/or utilized with several equally important disclaimers in mind.

Almost all of our current knowledge about fever-related responses of the body's molecular, energy-supplying mechanisms has been gained by studying acute febrile states. There is no certainty that this information can be transferred to subacute or chronic febrile problems. Most of the cellular data relating to fever has been obtained during infectious illnesses or toxemias imposed on laboratory animals, but comparable animal models have not been developed to study chronic febrile states. In this regard, little is known about the mechanisms which allow the body to generate a febrile response during periods when energy-yielding substrates have been severely depleted.

While much has been learned about gluconeogenesis, ketogenesis, and amino acid metabolism during febrile illnesses, much less is known about possible changes in fatty acid metabolism and the factors that regulate the release from adipose tissues during fever of these major sources of metabolizable energy which can be used by numerous types of cells

throughout the body.

Although hormonal factors play important roles in helping to regulate cellular metabolism during periods of fever, little is yet known about other poorly defined humoral and neurological mechanisms that appear to be responsible for initiating a febrile response, and at the same time, for orchestrating the complex, multi-tissue metabolic changes that accompany the onset of fever.

Finally, little is yet known about the role or purpose of fever during disease processes. While new evidence has emerged to suggest that febrile responses may have survival value (Keusch, 1977), the metabolic costs to a patient are sizable, especially if high, unremitting fevers are allowed to persist.

ENDOCRINE INFLUENCES

Hormonal responses during both febrile infections (Beisel, 1972, 1975, 1977) and artifically induced fever (Beisel et al, 1968) include an increased output of adrenal glucocorticoid hormones (Beisel and Rapoport, 1969). An accelerated cellular uptake and metabolism of thyroidal hormones seems to occur in many infections accompanied by a decrease in triiodothyronine concentrations and an increase in "reverse" triiodothyronine values in peripheral blood (Chopra et al, 1975). The catecholamines may be secreted in increased amounts (Groves et al, 1973; Wilmore et al, 1974) and growth hormone may be released from the anterior pituitary gland (Davidson et al, 1971). Importantly, the pancreatic islets of Langerhans release both insulin and glucagon into the plasma (Rayfield et al, 1973; Rocha et al, 1973; Blackard et al,

1976) and increased concentrations of these hormones can be measured in portal vein as well as peripheral blood (Curnow et al, 1976).

SUBSTRATE AVAILABILITY

During infectious fevers, there appears to be a continued cellular ability to utilize all energy-yielding substrates that normally serve to maintain cellular functions. These include a continued use of free fatty acids as a major fuel for cellular functions, an increased oxidation of glucose and the branched-chain amino acids, but, in contrast, a diminished use of ketone fuels. Substrates such as glycerol, lactic acid, pyruvic acid, and certain of the amino acids such as alanine and glutamine continue to be used for the purposes of gluconeogenesis (O'Donnell et al, 1976).

During febrile infections, the ketone bodies can be utilized as sources of metabolizable cellular energy if they are present. However, in contrast to the markedly increased utilization of ketones as a major form of body fuel during periods of starvation (Cahill, 1976), there appears to be diminished production of ketone bodies within the liver during the course of febrile infections, despite the occurrence of total or partial starvation during the illness (Neufeld et al, 1977).

In contrast, the uptake and utilization of branched-chain amino acids as direct sources of metabolizable energy appears to be accelerated within skeletal muscle cells (Imamura et al, 1975; O'Donnell et al, 1976; Wannemacher et al, 1978). This process, in turn, provides carbon and nitrogen groups which allow muscle cells to synthesize the gluconeogenic amino acids alanine and glutamine. Following their release from muscle,

these amino acids can be utilized as key substrate for gluconeogenesis in other body cells, such as the liver and kidney. The liver accelerates its uptake of most amino acids during periods of fever (Wannemacher, 1977). This influx is sufficient to cause a decrease in plasma amino acid concentrations (See Figure 1).

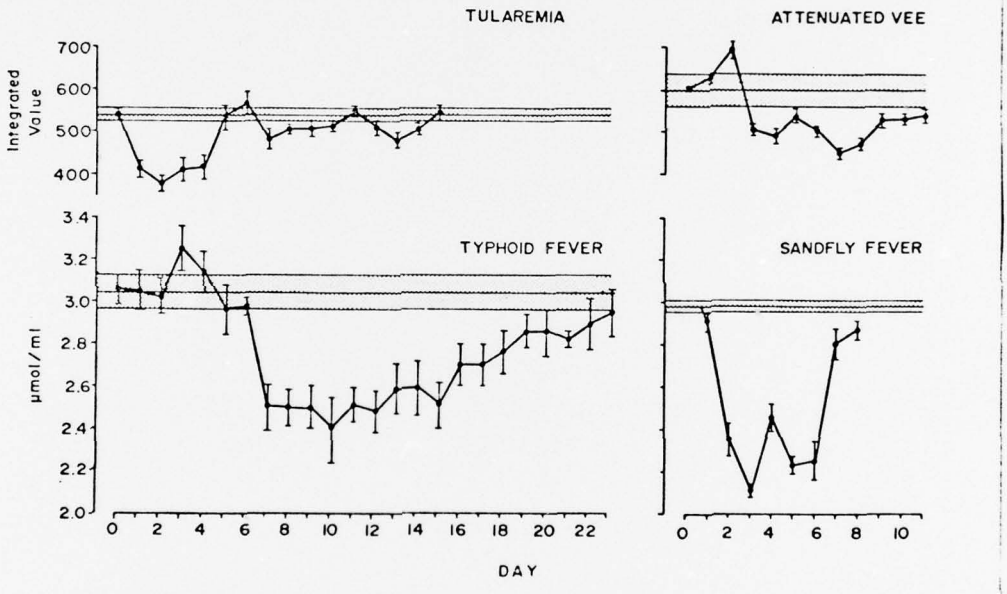

FIGURE 1. CHANGES IN PLASMA TOTAL FREE AMINO ACID CONCENTRATIONS DURING INDUCED FEBRILE INFECTIONS. Daily changes in mean (± S.E.) values are shown in comparison to baseline values (horizontal bands) obtained in the same groups of volunteers prior to their inoculation with infectious organisms (Reproduced from Beisel, 1972). The decline in total plasma values was influenced by the onset time, severity and duration of fever. The greatest decline occurred in the branched-chain amino acids, with most other plasma amino acids participating to lesser degrees (Wannemacher et al, 1972 and 1976); in contrast, phenylalanine and sometimes tryptophan values became elevated during the fever.

During the early stages of fever, the liver uses all of its usual substrates for producing glucose, including lactate, pyruvate, glycerol, alanine and other gluconeogenic amino acids. However, the ratio among these substrates is altered during infection to reflect the increased utilization of alanine (which is supplied predominantly by skeletal muscle) and lactate (which is released in increased amounts from body cells during states of metabolic acidosis). Lactate production increases when cells are involved in an inflammatory response or suffer from decreased availability of oxygen.

In the liver, the carbon atoms derived from lactate and pyruvate contribute only to the recycling of glucose, whereas, in contrast, the carbon derived from alanine or other amino acids can replace the glucose lost by oxidation (Wannemacher, 1977).

ACCELERATED GLUCONEOGENESIS

Using radioisotopic techniques, Long and his colleagues (1976), working in the laboratories of Dr. Kinney at Columbia University, showed conclusively that the production of glucose was accelerated during septic fevers in surgical patients. The increase in glucose production was under such potent control mechanisms in these individuals that it was not inhibited by intravenous infusions of 5% dextrose. Other studies in laboratory animals have consistently confirmed the occurrence of accelerated gluconeogenesis and glycogenolysis in the liver (Long, 1977).

Glycogenolysis and gluconeogenesis are both accelerated during septic fever by the combined actions of several hormones acting to

stimulate adenylate cyclase and other enzymes required for the breakdown of hepatic glycogen and the synthesis of glucose, and, in addition, by the increased availability within the liver of the necessary gluconeogenic substrates. The increased flux of free amino acids from muscle to plasma to liver is of key importance (Wannemacher, 1977).

Plasma concentrations of all hormones known to stimulate hepatic gluconeogenesis may increase during fever (George et al, 1974). An important additional hormonal increase occurs during septic fever, manifested by an enhanced secretion of pancreatic insulin. Increased insulin secretion occurs in direct contrast to the decrease in insulin output that is typical of the adaptation of the host to simple starvation (Cahill, 1976). The increase in portal vein insulin concentrations should stimulate hepatic glycogenesis and lipogenesis and inhibit gluconeogenesis and ketogenesis. Despite the presence of somewhat higher insulin concentrations in plasma during septic fever, the increases in glucagon and catecholamine secretion appear sufficient to stimulate the accelerated hepatic production and release of glucose through their ability to activate hepatic adenylate cyclase (Curnow et al, 1976).

The contribution of alanine to the accelerated gluconeogenic response has been shown by using radioactively labeled alanine during septic fevers in both patients and experimental animals. The accelerated gluconeogenesis using alanine as a major substrate was not suppressed in septic fevers by an infusion of 5% glucose (Long et al, 1976). The oxidation of alanine appeared equal in magnitude to that observed in normal subjects.

Studies using radioactive glucose and alanine in septic rhesus monkeys (Wannemacher et al, 1977 and 1978) confirmed these findings in patients with septic fevers. In monkeys subjected to experimentally induced, nonlethal pneumococcal sepsis, the production of glucose increased from 7.2 to 11.4 mg/kg/min, while its utilization rate increased from 7.3 to 11.5 mg/kg/min. At the same time, the endogenous synthesis of alanine increased from 0.53 to 0.60 mmol/kg/hr, while the utilization rate for alanine increased from 0.53 to 0.87 mmol/kg/hr. The use of the newly synthesized alanine for manufacturing glucose increased from 38 to 77%. Similarly, the acute stages of pneumococcal septic fever in rats led to accelerated rates of glucose synthesis approximately twice those found in control rats (Wannemacher et al, 1977).

PERIPHERAL GLUCOSE METABOLISM

It is taught clinically that insulinopenic "juvenile" diabetic patients are likely to spill sugar in their urine and require extra amounts of insulin if they develop fever. Studies performed in man indicate that there is a slowed rate of disappearance of infused glucose from the blood of febrile patients with an early infection (Shambaugh and Beisel, 1967, Rayfield et al, 1973). In these studies, the kinetic disappearance constant, K, for glucose disappearance, was sufficiently slowed so as to resemble values measured in patients with diabetes mellitus. These facts were initially interpreted as signs of transient insulin resistance. They can now best be explained by the accelerated hepatic synthesis of new glucose with expansion of the glucose pool size.

As implied earlier, the metabolic machinery for maintaining an increase in glucose concentrations may fail in severe, lethal illnesses (Wilmore, 1977). When this occurs in laboratory animals, the falling blood glucose values are accompanied by a plunge of body temperatures into the subnormal range. Mechanistically, these terminal catastropic events could occur if hepatic enzymatic mechanisms for producing glucose fail or are destroyed, as in severe, viral hepatitis (Felig et al, 1970), overwhelming endotoxemia (Berry et al, 1950; Filkins and Cornell, 1974), or severe yellow fever (Wakeman and Morrill, 1931). Similarly, severe hypoglycemia and hypothermia may occur in septic infections if body protein stores are inadequate to maintain an adequate continuing supply of amino acids for use as substrates for gluconeogenesis. Such an event is seen clinically in neonatal sepsis (Yeung, 1970) due to the fact that newborn infants are born with very little skeletal muscle and do not possess an adequate pool of metabolizable somatic protein to overcome such an emergency. Also, patients with severe protein-energy malnutrition or aged individuals who have lost much of their protein reserves can also experience hypothermia rather than fever when severe infections occur.

The kinetic studies of Long et al (1976) showed a three-fold increase in pool size, turnover rate, and oxidation rates of ^{14}C-labeled glucose infused in patients with septic fever. Further, a mathematical model based on these data, as interpreted by Long et al (1976), suggested that some of the carbon derived from glucose was being used to manufacture fat molecules in the febrile septic patients. An acceleration of lipogenesis was also suggested in these subjects on the

basis of their greater increase in respiratory quotient (RQ) values during periods when they were receiving glucose, in comparison to the RQ values observed during glucose infusions in normal control subjects.

Earlier workers had also reported an increase in RQ during the early stages of fever (Barr et al, 1922; Alschule and Freedberg, 1945). Although such increases could be interpreted as evidence for an increased proportional oxidation of glucose, it is also possible that the higher RQ values may merely reflect the occurrence of respiratory hyperventilation, which is consistently seen in patients during periods of sharply rising body temperatures. Respiratory quotient values are known to increase when a normal patient hyperventilates purposefully for a period of time. Another potential problem in evaluating measurements based on respiratory gas exchange is the impairment of oxygen uptake caused by acute pneumonic consolidation (Korotzer et al, 1978).

NITROGEN METABOLISM

Alanine and glutamine are released from skeletal muscle during fasting or septic fever in amounts that are far greater than can be accounted for solely by the proteolysis of muscle protein (Wannemacher, 1977). Excessive release, however, can be explained by the synthesis within muscle of these gluconeogenic amino acids using nitrogen derived from the oxidation of the branched-chain amino acids and carbon derived from other amino acids or pyruvate. Alanine is the predominant gluconeogenic amino acid in man as well as an important vehicle for

the transport of nitrogen from muscle to liver (Felig, 1973). Glutamine can enter the liver to be used for gluconeogenesis, can enter the kidney to be utilized for gluconeogenesis, and concomitantly, for the synthesis of ammonia, or can be taken up by intestinal mucosal cells (Wannemacher, 1977).

The increased utilization of body proteins as substrates for the synthesis of glucose could account for the continuing (or increased) losses of urinary nitrogen observed during febrile states. Nitrogen balance studies conducted during the course of experimentally induced infectious diseases show that nitrogen deficits begin to occur shortly after the onset of fever (See Figure 2). A comparable loss of body nitrogen occurs if fever is induced by noninfectious measures such as placing the subject in a hot, humid atmosphere (See Figure 3).

Cumulative nitrogen losses from the body vary in magnitude with the intensity and duration of febrile illnesses and, as shown in Figure 4, are not reaccumulated quickly after fever has subsided. Balance studies reported by Howard et al (1946) in patients inoculated with vivax malarial parasites for therapy of neurosyphilis showed the progressive development of a disassociation between continuing febrile bouts and the magnitude of daily nitrogen losses. As shown in Figure 4, fever spikes of typical magnitude continued to occur throughout the malaria study, but daily nitrogen losses diminished gradually until the patients entered a new state of nitrogen equilibrium.

Urea is the predominant component of urinary nitrogen excreted during febrile infections (See Figure 5) in man or experimental animals.

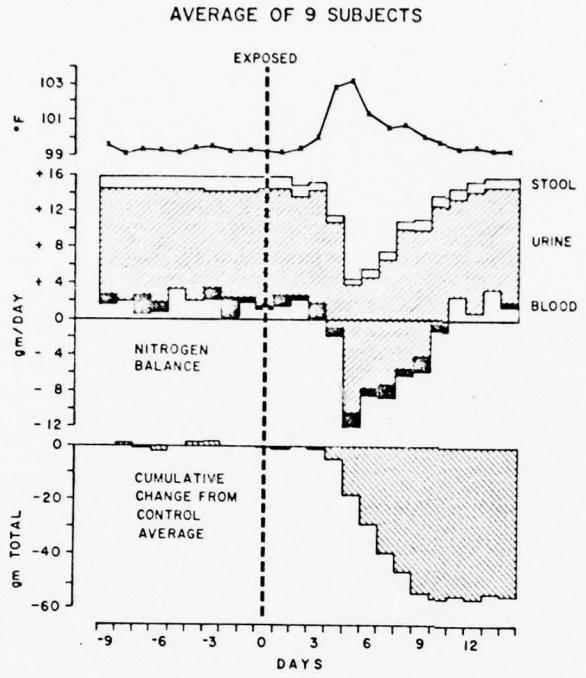

FIGURE 2. NITROGEN BALANCE DATA AS RELATED TO THE FEVER CURVE IN EXPERIMENTALLY INDUCED TULAREMIA. (Reproduced from Beisel et al, 1967.) To the top is shown the fever curve before and after exposure to the infecting organisms on Day 0 (vertical dashed line). Nitrogen balance is shown in the middle, and cumulative changes from the average balance value of all baseline control days are shown at the bottom.

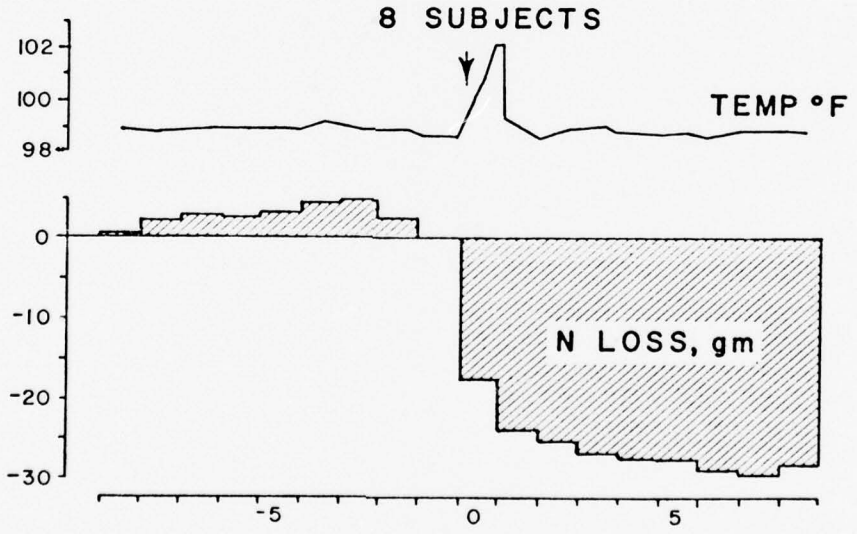

FIGURE 3. CUMULATIVE NITROGEN BALANCE CHANGES AFTER INDUCED HYPERTHERMIA. (Reproduced from Beisel et al, 1968.) Mean balance data are shown from eight subjects with fever induced by a hot, humid atmosphere during a 24-hr period. The increase in body temperature was controlled so as to mimic the exact pattern of fever measured in the patients with tularemia depicted in Figure 2.

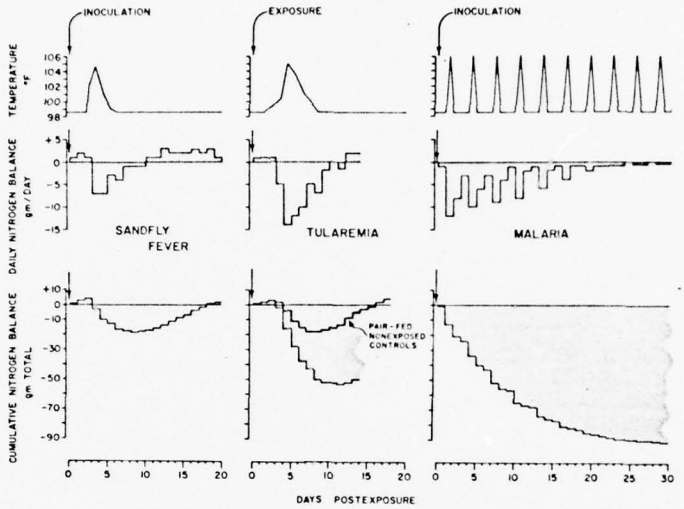

FIGURE 4. COMPARISON OF FEVER CURVES WITH NITROGEN BALANCE DATA IN SANDFLY FEVER, TULAREMIA, AND MALARIA. (Reproduced from Beisel, 1977.) Note the eventual disassociation between fever and daily nitrogen losses after 5-7 malarial paroxysms, the far greater cumulative nitrogen losses in febrile tularemia patients than in pair-fed control subjects, and the prolonged period required to reaccumulate the body nitrogen lost during the brief febrile period of sandfly fever. Malaria data are adapted from Howard et al (1946).

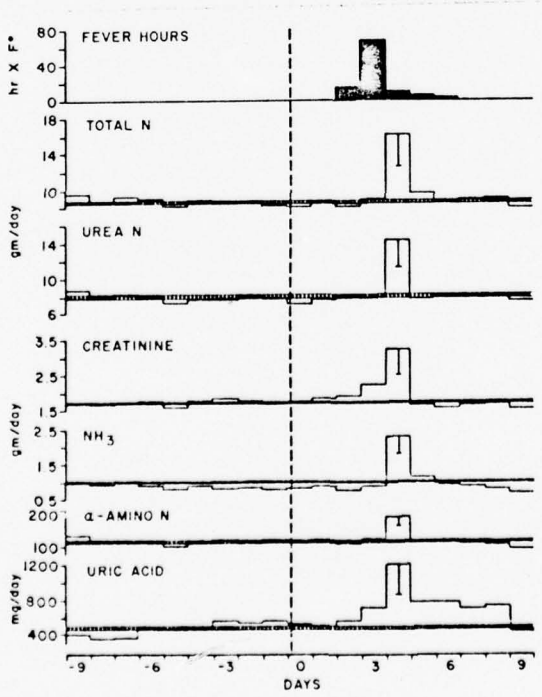

FIGURE 5. PATTERNS OF URINARY NITROGEN EXCRETION IN SANDFLY FEVER. (Reproduced from Beisel et al, 1972.) Data from eight patients are shown in comparison to baseline control mean ± S.E. values (horizontal bands). Inoculation of virus was on Day 0 (vertical dashed line); average daily fever hours are shown to the top.

The accentuated loss of urea via the kidney can primarily be accounted for by the continued or accelerated synthesis of urea within the liver. During gluconeogenesis from alanine, amino groups which are liberated contribute importantly to this synthesis of urea through the metabolic pathways and enzymatic machinery normally used for ureagenesis. The increased utilization of amino acids as substrates for gluconeogenesis appears sufficiently large to account for fever-related increases in urea excretion.

Similarly, acceleration of ammonia synthesis in the kidney, from nitrogen derived from glutamate, appears to explain the increased urinary loss of ammonia observed in febrile states (Cahill and Aoki, 1975). As shown in Figure 6, the pattern, timing, and duration of increases in individual components of urinary nitrogen were quite similar when determined in patients experiencing a single day of

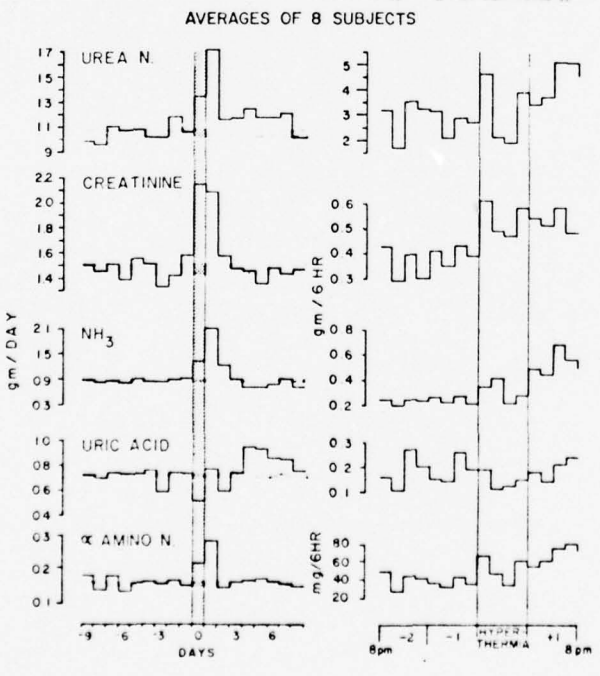

FIGURE 6. URINARY NITROGEN CHANGES FOLLOWING A SINGLE DAY OF ARTIFICIALLY INDUCED HYPERTHERMIA. (Reproduced from Beisel et al, 1968). Note the similarity with nitrogen losses measured in the fever caused by sandfly fever virus, Figure 5.

artificially induced hyperthermia in comparison to a comparable brief fever due to a benign viral infection as shown in Figure 5.

Approximately 35 to 40 kcal are required for the synthesis of one mole of urea. Thus, the use of amino acid substrates for gluconeogenesis consumes more energy than does the use of lactate as a substrate. On a molar basis, amino acids supply 20% less energy than the equivalent amount of glucose. Therefore, the expenditure of body protein as an energy source is a relatively inefficient process. In contrast, body fat is a far more efficient source of energy.

FATTY ACID METABOLISM

Fatty acids are utilized by the body as principal sources of energy in fasting conditions, including interprandial and overnight periods (Cahill, 1976). Although relatively little detailed information is available concerning changes in the rates or extent of free fatty acid utilization as a direct source of cellular fuel during periods of fever, some postulations can be made as illustrated schematically in Figure 7.

Free fatty acid concentrations in plasma have been found to decrease in most febrile infections (Beisel and Fiser, 1970; Lees et al, 1972; Coran et al, 1972; Blackburn, 1977.) This could be interpreted as an indication that either fewer free fatty acids were being released from storage depots, or that plasma free fatty acids were being taken up by the liver and other tissues at an accelerated rate and used to produce cellular energy. The reported decline in plasma free fatty acid values in febrile infections may also be related to the typical, infection

induced decline in plasma concentrations of albumin, the major transport protein for free fatty acids.

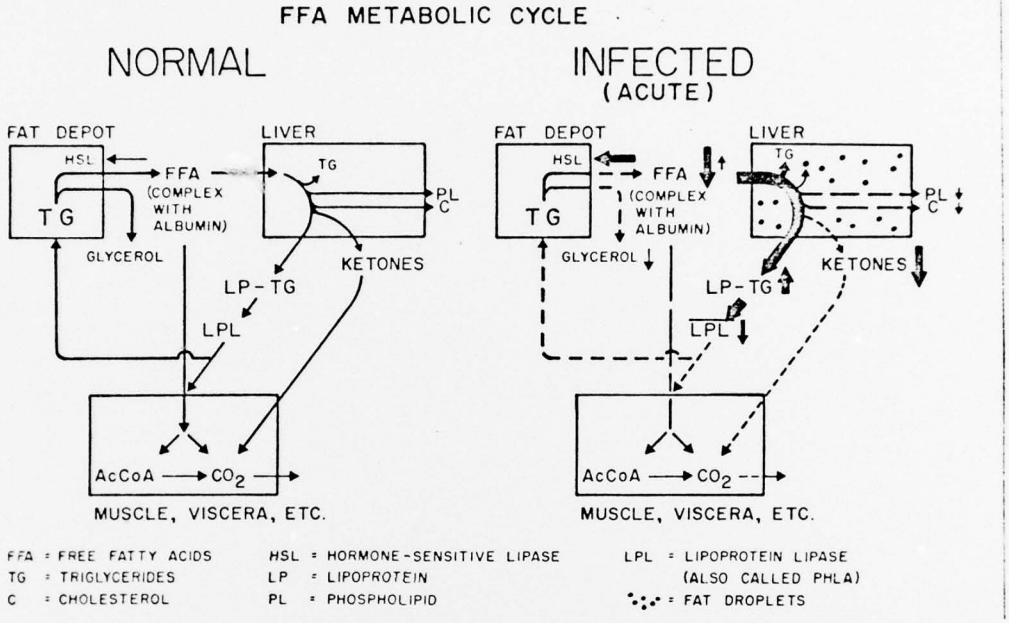

FIGURE 7. SCHEMATIC COMPARISON OF FREE FATTY ACID METABOLISM IN FASTED NORMAL AND FASTED ACUTELY INFECTED FEBRILE ANIMALS. Arrow show direction and magnitude of alterations in plasma components; pathway increases are shown with wide lines and decreases with dotted lines.

In other studies performed during gram-negative septic fevers (Gallin et al, 1969), the plasma concentrations of free fatty acids and most other lipids were found to increase rather than to decrease. This could imply that the release of free fatty acids from adipose depots was accelerated, or, on the other hand, that their utilization by the liver and the peripheral tissues was inhibited.

The apparent increase in serum insulin concentrations during febrile states should inhibit the release of free fatty acids from adipose depots, inasmuch as insulin is known to stimulate the uptake

of free fatty acids by lipocytes and to inhibit their release from these cells.

On the other hand, the uptake of free fatty acid is accelerated by liver cells during endotoxemic fever in monkeys (Fiser et al, 1974). while at the same time, the liver accelerates its conversion of free fatty acids into triglycerides. Such data would explain depressed free fatty acid values in plasma, but would imply that the fatty acids taken up by the liver were not being utilized as direct sources of metabolizable energy. An acceleration of lipogenesis within the liver is also implied by the studies of hepatocyte functions conducted during febrile infections in laboratory animals by Canonico and his colleagues (1977a and 1977b), and is compatible with the interpretation of glucose kinetic data of Long et al (1976).

During periods of fasting in normal subjects or experimental animals, the hepatic uptake of free fatty acids is accelerated (Cahill, 1976). Intrahepatic free fatty acids of fasting subjects are enzymatically complexed to carnitine and the resultant fatty acid-acylcarnitine complexes are then transported into the mitochondria where they are oxidized to acetyl CoA which can be synthesized into ketone bodies for prompt secretion into the plasma to serve as a metabolic fuel for peripheral body cells. During the ketogenic response to fasting, few fatty acids are synthesized within the liver and the conversion of fatty acids to triglycerides is minimized (Cahill, 1976). On the other hand, despite the reduction of food intake during febrile infections, fatty acids are actively synthesized

within hepatocytes and many are converted into triglycerides. Some of the triglycerides become sequestered within hepatocyte fat droplets, causing fatty metamorphosis of these cells. In addition, the hepatic excretion of newly synthesized triglycerides, cholesterol, and phospholipids is accelerated (Beisel and Fiser, 1970; Lees et al, 1972), while, at the same time, the ketone production tends to be inhibited.

The contribution of brown fat to heat production may be relatively large in newborn infants (Smith and Horwitz, 1969), but little is known about the potential usefulness of this energy source during periods of fever.

KETOGENESIS

Based on the extensive studies by Neufeld and his colleagues (1976) of ketogenesis during febrile states and the data on peripheral blood ketone concentrations in febrile patients (Blackburn, 1977), it now seems evident that acute febrile illnesses are accompanied by a diminished rate of production of ketone bodies. Ketogenesis was found to be inhibited during a variety of febrile infections in laboratory animals, including pneumococcal and tularemia infections, Venezuelan equine encephalomyelitis, and endotoxin fevers, or the production of sterile turpentine abscesses (Neufeld et al, 1978). If starvation ketosis was present at the onset of a study in these animals, it disappeared during the development of the febrile period. Extensive biochemical studies have failed to reveal the presence of an enzymatic defect or the disruption of a normal molecular mechanism that could account for the inhibition of ketogenesis during these febrile states.

Although the transport of long-chain fatty acids into the mitochondria was somewhat depressed in livers of febrile rats (Pace et al, 1977) there was no impairment in short-chain fatty acid movement into the mitochondria, and no lack of carnitine or oxidative capacity of the mitochondria. Further, the febrile animals with inhibited ketogenesis could still utilize intravenously infused ketones in a rapid and complete manner.

Studies conducted by Neufeld and his colleagues (1978) in laboratory rats with experimentally induced diabetes led to the conclusion that the increase in insulin secretion during febrile states could account, in large part, for the inhibition of ketogenesis. When rats were made diabetic by the administration of streptozoticin, and then given small maintenance doses of insulin, up to 5 units per day, to maintain the levels of peripheral ketone bodies as close as possible to the normal semifasted state, the subsequent induction of febrile pneumococcal sepsis led to a ketogenic response that was equivalent to that observed in rats deprived of food. Thus, febrile rats that did not have the ability to secrete insulin did not show an inhibition of ketone body production. The present data suggest that reduced ketone production in the febrile host may be the combined result of decreased fatty acid supply and depressed utilization of these substrates by the liver for ketone synthesis. The role that insulin and glucagon play in mediating this response during febrile states has not been completely elucidated.

SUMMARY

1. During fever, the body continues to utilize its normal molecular machinery for generating energy, with fatty acids apparently serving as the major source of fuel.

2. In addition, the requirements for the extra metabolizable energy associated with the presence of fever are largely met by the accelerated hepatic synthesis of glucose. The need to synthesize larger quantities of glucose is filled principally by the use of amino acid substrates which are supplied by the catabolism of proteins in muscle and other somatic tissues and the synthesis of gluconeogenic amino acids within muscle.

3. Despite the concomitant presence of varying degrees of starvation in a febrile individual, ketone synthesis is depressed.

4. Little is known about fever-energy production relationships during states of protracted fever or in the presence of a severe depletion in body protein stores.

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This is an invited paper for oral presentation by Dr. Beisel at a Conference on "The Assessment of Energy Metabolism in Health and Disease," chaired by John M. Kinney, M.D., Hamish N. Munro, D.Sc., and Elsworth R. Buskirk, Ph.D., and sponsored by Ross Laboratories, a Division of Abbott Laboratories, (Continued)

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SUMMARY: 1. During fever, the body continues to utilize its normal molecular machinery for generating energy, with fatty acids apparently serving as the major source of fuel. 2. In addition, the requirements for the extra metabolizable energy associated with the presence of fever are largely met by the accelerated hepatic synthesis of glucose. The need to synthesize larger quantities of glucose is filled principally by the use of amino acid substrates which are supplied by the catabolism of proteins in muscle and other somatic tissues and the synthesis of gluconeogenic amino acids within muscle. 3. Despite

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20. the concomitant presence of varying degrees of starvation in a febrile individual, ketone synthesis is depressed. Little is known about fever-energy production relationships during states of protracted fever or in the presence of a severe depletion in body protein stores.